BRIEFING BOOK

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EXECUTIVE SUMMARY

This paper addresses the scientific and public health issues raised by the petition of Blue Cross of California to change drugs containing loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride from prescription to OTC status. As discussed below, there is not an adequate basis to support OTC use of these drugs at the present time. There are three major grounds for this conclusion.

1. The Blue Cross petition does not provide data of the type or rigor that is required to support an OTC switch.

   The petition relies solely on anecdotal safety evidence from a Canadian adverse drug reaction database and a meta-analysis that inappropriately combines data from clinical trials with differing methodologies. Further data pertinent to actual OTC use would have to be generated and additional analyses conducted for proper assessment of safe and effective use without a physician's supervision. This would include prospective studies to investigate the expected therapeutic index for drug use in an OTC setting, as well as estimates and evaluation of the probability of various adverse outcomes.

2. The complexity of proper diagnosis and treatment of allergic diseases, as well as associated comorbid conditions, suggests that self-care may often be inappropriate and that labeling to ensure safe and effective OTC use cannot be developed without further study.

   Prescription status may well be necessary to protect and optimize public health. As compared to when earlier antihistamines were made available OTC, there is a dramatically different understanding today of the seriousness of allergies, their pervasive effects on health and quality of life, and most notably, their very high association with other serious comorbidities. In particular, a strong relationship with asthma has now been documented, as well as an association with sinusitis and otitis. A thorough medical evaluation with identification of environmental allergens and clinical or subclinical comorbid conditions is essential for optimal treatment outcomes. To ensure best immediate outcomes and possibly diminish long-term sequelae, multiple guidelines have been developed by U.S. and International expert bodies (e.g. ARIA [WHO], NHLBI, Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology, etc.). Each of these has recommended that the appropriate approach to management of allergies and other conditions, particularly asthma, includes a disease management, treatment, and monitoring/support plan that incorporates prevention (e.g., changes in home and occupational exposure and in lifestyle), as well as a coordinated pharmaceutical approach.

Physician oversight is also critical to ensuring that patients do not mistakenly self-diagnose symptoms as allergies that actually reflect a different disease requiring different intervention. A full analysis of OTC label comprehension, in-use evaluation, and outcomes evaluation are essential to estimate the potential for inappropriate use in an OTC setting and to quantify potential risks.

3. The safety profile of second-generation antihistamines in an OTC setting is not fully known.

   Although safety is well established for prescription use, significant issues require further study to ensure that equivalent safety would exist without a physician's care. The absence of a physician, pharmacist, or PBM system as an intermediary who would be aware of a patient's concomitant medications is a concern. The pharmacokinetic interaction and safety profile for each of the second-generation antihistamines is different and each of the antihistamines must be considered and evaluated independently.

   Other aspects of the pharmacologic profile of these drugs also warrant more specific evaluation, particularly were the drugs to be used without physician oversight. The history of this class of drugs is one in which unexpected interactions have been discovered many years after use by millions of patients. Loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride should not be changed from prescription to OTC status until additional data exist to address these and other questions.

Schering-Plough has developed many significant prescription products, as well as switched a number of drugs to OTC status. On these occasions we have worked with FDA and produced a quality dossier to support an OTC switch. For each of these switches we also worked closely with the medical community and were confident that OTC status was an appropriate designation.

We do not believe, at the present time, with the existing data that it is appropriate for loratadine to be switched to OTC. Before the Agency considers such a switch, we believe the issues raised in this paper need to be addressed. This may involve conducting a number of studies, including the following:

- Outcome studies in patients requiring concomitant medications. Does the OTC availability of a mainstay R_x therapy in such patients lead to worse medical care or outcomes?
- Assessment of the long-term consequences of removing patients from the disease management approach of the current medical system. Loratadine is now prescribed as part of a chronic disease management process, but OTC use is necessarily oriented toward acute symptomatic relief.
- Assessment of label comprehension under conditions of use.
- Actual-use study to test appropriate self selection and use.

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Making these drugs OTC at the present time would also raise serious legal and public policy questions. Any switch over a sponsor's objections would constitute an unprecedented departure from past agency policy and implicate the sponsor's statutory and constitutional rights. Such a decision should also receive careful review as a matter of public policy. The Blue Cross petition is motivated by the petitioner's desire to shift costs from third party payers to allergy sufferers. Moving these antihistamines to OTC status would shift costs from health insurers to patients. This is likely to have a detrimental impact on access in general and in particular on access for groups that can least afford to pay for medications out-of-pocket. Moreover, the Canadian experience shows that taking second generation antihistamines OTC does not significantly decrease the use of first generation products. These legal and policy issues are beyond the scope of this paper, but nonetheless remain a critical component of the overall consideration of the Blue Cross petition.

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1. BACKGROUND

1.1. Claritin® (loratadine) and the Treatment of Allergic Diseases

Claritin® (loratadine) is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity. It is one of the so-called "second-generation" antihistamines and is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR).[a]

SAR was historically thought of as inconsequential and its treatment with antihistamines straightforward. However, recent scientific advances have provided greater appreciation of the seriousness of the disease, and the complexity of the disease mechanisms and treatment considerations. Last year FDA introduced a draft guidance on clinical development programs for allergic rhinitis by stating, "[i]nformation about the pathophysiology and treatment of allergic rhinitis and its subtypes . . . has grown markedly in the past decade."[1]

1.2. The Seriousness and Complexity of Allergic Diseases

Allergies are the sixth leading cause of chronic disease in the United States.[2] Estimates from a skin test survey suggest that allergies affect approximately 30% of the U.S. population,[3] including 10% to 30% of all adults [4–8] and up to 40% of all children.[9] At least 35.9 million people in the United States have been estimated to suffer from seasonal allergic rhinitis.[10] These statistics support reports that the U.S. is experiencing an "allergy epidemic."[11]

Children in particular are widely affected by allergic rhinitis. Approximately 10% to 30% of school-age children are estimated to have allergic rhinitis,[12,13] and nationwide

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a: Allergic rhinitis describes the symptoms of nasal irritation or inflammation that occur when exposure to an allergen triggers the release of histamines, which dilate the small blood vessels of the nose and cause fluids to leak into the surrounding tissues, including those of the nose. Allergic rhinitis is divided into two subtypes: seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

children with allergic conditions are estimated to have 2 million school absences per year. Affected children may exhibit learning and behavioral problems.[14-16]

It is also now recognized that a number of chemical mediators play a role in allergic rhinitis, including histamine, leukotrienes (LTC_4, LTD_4, and LTE_4), kinins, prostaglandins, chemotactic factors, neuropeptides (e.g., substance P, CGRP, VIP), interleukins -1, -5, -6, -8, and tumor necrosis factor-α.

It has also been established that allergic rhinitis is associated with serious comorbid conditions, including allergic asthma,[5,17-19] acute and chronic sinusitis,[20-23] otitis media and Eustachian tube dysfunction,[24] and allergic conjunctivitis.[25] Comorbidities are significant because they contribute to the disease burden of allergy patients, and they can increase costs associated with treatment of allergic rhinitis. Since data suggest that allergic rhinitis often precedes and may worsen related comorbidities,[26] allergists view early control of allergic rhinitis symptoms as a key means of avoiding or decreasing the severity of these other conditions.[4]

Allergic rhinitis and asthma share the same immunopathogenesis. Both diseases are inflammatory, and the mucosa of the upper and lower airways are contiguous. As many as 78% of asthma patients have nasal symptoms,[17,27,28] and as many as 38% of allergic rhinitis patients have asthma.[4,28] As evidence of how this has translated into current clinical practice, in the year 2000, almost 3 million prescriptions for loratadine were co-prescribed with prescriptions for asthma medications, for approximately 1.2 million patients with asthma.[29] Clinical study reports have supported the premise that treating allergic inflammation in the nose may reduce asthma symptoms and lower airway hyper-responsiveness.[30–34]

1.3. Marketing Experience with Loratadine

Loratadine is a prescription-only medication in most markets, including the United States and many major developed countries, such as France, Italy, and Spain. Loratadine is prescription-only in approximately 80 countries and non-prescription in 21 countries. However, in 17 of 21 non-prescription countries, loratadine is available only “behind the counter” (BTC) of a pharmacy, and can only be sold under the supervision of a pharmacist. Loratadine is available without medical supervision in only four countries (Canada, Australia, New Zealand, and the Philippines).

In most countries where loratadine is available BTC/OTC, it is also available as a prescription drug, and non-prescription sales rarely account for more than 20% of total sales. This indicates that physician treatment and supervision continues as a critical element of proper medical care, and that OTC or BTC status outside the U.S. is generally only an additional access route.

OTC status as practiced in the United States would result in the effective termination of any reimbursement for antihistamines and reduction in direct physician care. The financial incentives driving patients under OTC status would be either to avoid seeing a physician and self-medicate, or to try to obtain other prescription drugs for which their costs are reimbursed. This could result in prescribing decisions being driven by reimbursement considerations, rather than those recommended by evidence-based treatment guidelines.

1.4. Considerations for OTC Switch

In light of the current understanding of allergies as a complex immunological response frequently associated with comorbid diseases,[35–38] careful physician management and oversight is critical to proper patient care.[4,5,25,39,40] Switching the leading allergy therapies from prescription to OTC status would unavoidably undermine the critical role now played by physicians in diagnosis and treatment.

Given the recognized allergy epidemic, the complexity of allergy and comorbid diseases, and the increased recognition of patient-safety issues related to overuse, underuse, and misuse of medication,[41–45] now is not the time to drive allergy patients further away from the physician.

Such a significant change should only be made after thorough study of the likely use and potential misuse of these drugs in an OTC setting. Moreover, the allergy population now taking R_x loratadine may not be the same as the current OTC population. As discussed below, data on these issues have not yet been developed. Accordingly, there is not an adequate scientific basis to remove loratadine and the other second-generation antihistamines from prescription status at this time.

2. DISCUSSION

2.1. The Data Provided by Blue Cross are Inadequate to Support an OTC Switch

Removal of the prescription-dispensing requirements for second-generation antihistamines is only appropriate if it can be demonstrated that the drugs are safe and effective for use as self-medication and do not present public health risks due to toxicity, other potential harmful effects, the method of use of the drugs, or the need for collateral measures in using the drugs (21 C.F.R. § 310.200(b)). As a matter of sound public health policy, as well as law, these demonstrations must be based on rigorous data of sufficient depth and breadth to evaluate the potential safety and effectiveness issues for these particular drugs. Sponsors seeking OTC switches in the past have been required to provide a large body of safety experience reflecting both clinical trial use and actual use, as well as updated scientific information developed since the time of initial NDA approval providing an enhanced understanding of the underlying disease, current medical practice, and/or the pharmacology of the drug.

Necessary data for a robust assessment of the likely use and potential misuse of the second-generation antihistamines in an OTC setting would include evidence addressing the following topics:

- Ability to accurately self-diagnose the condition
- Assessment of risk of initial misdiagnosis
- Assessment of label comprehension under conditions of use
- Assessment of risk of disease exacerbation or common comorbid conditions due to subsequent misdiagnosis
- Assessment of risk of incorrect dosing (voluntary and/or inadvertent)
- Assessment of potential outcomes of OTC use

The retroactive compilation of clinical outcome scores from controlled clinical trials under physician supervision is not adequate to support OTC use. Prospective data is required and should be generated based on the design of proper protocols or models that assess all aspects of clinical outcome, functional performance, and impact on disease state. An OTC drug's impact should be assessed as much as possible in an OTC setting, not as it

has been utilized as an R_x under a physician's supervision. Such methodologies have been developed over the past decade and tested in other OTC-switch scenarios, e.g., actual-use studies. It would be inconsistent with past Agency practice, and legally and scientifically inappropriate, to consider an OTC switch without a rigorous demonstration of appropriate outcomes based on such methodologies.

Viewed against these standards, the Blue Cross petition is clearly deficient. The only data provided by Blue Cross in its various submissions to the agency are 1) Canadian spontaneous adverse event reports from initial marketing to April 12, 1999, and 2) an "evidence report" consisting of an unpublished meta-analysis based on a literature search that purports to compare the safety and efficacy of first-generation and second-generation antihistamines for the treatment of allergic rhinitis.[a] No prospective data are cited, and the bulk of the information is derived from controlled trials and not actual use in an OTC setting. The particular meta-analysis methodologies employed are deeply flawed, combining data from grossly different study methodologies and disease settings. Such information is not of the type or rigor that can support an OTC switch.

2.1.1. Canadian Adverse Drug Reaction Report

The Canadian Bureau of Drug Surveillance's adverse drug reaction report (dated April 30, 1999) provides anecdotal evidence from postmarketing experience only, and cannot be relied upon to rule out potential safety issues. The reports are necessarily selective and incomplete. Accordingly, they do not provide a valid safety profile of the drugs in an OTC setting. This is true of postmarketing adverse event databases generally, and the Canadian database as well. In fact, the cover letter of the report provided by the Canadian Bureau of Drug Surveillance specifically warns not to rely on the report:

> *CAVEAT: Only a small proportion of suspected adverse reactions are reported to the program, consequently this information must not be used to estimate the incidence of adverse reactions.*

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a: The original Blue Cross petition (dated 7/21/98) consisted of a two-page letter with six bulleted statements and no corroboration or references requesting that FDA exempt loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride from the prescription requirement.

These Canadian data are thus of questionable value, at best, and are short of the type of data that would be needed to show that loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride could be used safely without a physician's supervision.

2.1.2. Meta-Analysis

Meta-analysis is a valid statistical approach for clinical and epidemiologic research, and indeed was utilized very effectively by FDA in its previous consideration of a "cold" indication for antihistamines.[46,47] However, the meta-analysis provided to support this Blue Cross petition (dated October 4, 2000) does not meet that standard of quality or rigor. The meta-analysis is flawed, and the methodology is inappropriate for a valid meta-analysis for the following reasons:

- The conclusion of the analysis, "these findings suggest comparable efficacy between first and second generation antihistamines", is based on a comparison of chlorpheniramine and terfenadine in five studies with a total of 402 patients, and disregards over 30 randomized controlled clinical trials and information on other first- or second- generation antihistamines. Two hundred patients per treatment group are inadequate to statistically compare two active-treatment groups in this class. In addition, potentially pertinent information on other relevant antihistamines, both first and second generation, are not included.
- The study designs of the trials included in the meta-analysis differ in too many respects to permit proper combination of data. The meta-analysis mixes trials designed to assess SAR and PAR with trials designed to address onset of action and prophylaxis of SAR. Some studies included a placebo run-in phase and some did not, and the studies are of variable treatment duration (1 day to 6 weeks). The studies occurred over very different time periods, covering some 20 years. Some studies included doses that were four times the labeled dose.
- CDER has recently issued a draft guidance document for industry regarding clinical development programs for drug products for allergic rhinitis.[1] The meta-analysis does not use endpoints considered acceptable under this guidance for relevant interpretation of allergic rhinitis studies.
    - The meta-analysis uses primarily the Global Efficacy Evaluation endpoint, which is no longer considered a suitable endpoint for allergic rhinitis trials.
    - The Total Symptom Score (TSS) endpoint is used in some analyses. However, different symptoms are used in different studies, and there is no explanation of how this discrepancy was addressed methodologically. Additionally, the TSS analysis does not use change from baseline, which is the appropriate methodology.[1]

- Patient-rated scores are preferred as the primary measure of effectiveness. [1] In the meta-analysis, some study scores were evaluated by the physician and others by the patient.

Because of these flaws, the meta-analysis presented by Blue Cross does not provide a basis for drawing valid conclusions about the safe and effective OTC use of loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride. Even without these flaws, the data would be of very limited value because the data were all obtained from controlled clinical trial settings. Information projecting the use of these products in an unsupervised OTC setting is essential for OTC consideration, including actual data or appropriate models projecting the outcome of drug use without physician oversight. Such data should also provide robust analyses of outcomes, and should address usage in patients with comorbidities, such as asthma.

2.2. Allergies May Not Be Appropriately Treated Without Physician Supervision

Allergies are more prevalent than ever before.[5,11,48] A number of scientific and lay reviews have warned that we are now experiencing an allergy epidemic. At the same time, we are only beginning to understand the complexity of allergic diseases and their relationship to other diseases. Both environmental and genetic influences on allergies are being discovered that can shape diagnosis and treatment in particular cases.[9,49] Suboptimal treatment of allergic disease may worsen comorbid diseases,[50] and the failure to differentiate allergic disorders from other diseases could have serious consequences. These concerns suggest that patients are best treated under a physician's care, and that real risks could arise if patients are encouraged to self-diagnose and self-medicate. At a minimum, careful additional study is warranted to determine whether appropriate labeling could properly manage these risks before additional allergy medicines are moved OTC.

2.2.1. Allergies Can be a Complex Disease to Diagnose and Treat

The development of allergic disease may be influenced by genetic susceptibility, environment, and the presence of other risk factors (e.g., passive smoke exposure).[9,49,51] Diagnostic evaluation, including specific testing, is designed to confirm the allergic

diagnosis, differentiate allergic disorders from other diseases, uncover previously unsuspected allergens, and guide treatment.[4,5,25] Allergic disease depends on allergen sensitization, continued allergen exposure, and other environmental irritants – each is a target for avoidance or control. [4,5,25]

The role of allergen avoidance (e.g., food allergies, drug allergies,[52] and occupational exposure) may best be detected, implemented, and repetitively reinforced by a physician.[4] In many instances, allergen avoidance may be only partially practical, while in other instances allergen avoidance can play a critical role.

Pharmacologic therapy for allergic diseases includes antihistamines, mast cell stabilizers, epinephrine, corticosteroids and decongestants. Allergen immunotherapy (allergy vaccine therapy) is also effective in appropriate patients.[4,25] Open communication between the healthcare provider and patient is critical and may make the difference between a chronic debilitating disease and an active healthy lifestyle.[53]

Proper treatment can be complicated. For example, in patients with severe SAR, antihistamines alone may not control the symptoms of SAR sufficiently. Effective treatment may require the addition of topical glucocorticosteroids or other prescription drugs. Patients self-medicating who do not experience sufficient symptom relief may tend to increase the antihistamine dose until they experience adverse effects from their medication.

2.2.2. Improper Treatment of Allergies Can Complicate or Worsen Comorbid Diseases

Allergies are now recognized as being frequently associated with serious comorbid diseases, such as asthma, sinusitis, and otitis media. Suboptimal treatment of allergies may complicate and worsen these comorbidities,[50] particularly asthma. Recent studies have suggested that allergic rhinitis occurs in 80% to 90% of asthmatics,[6] and the relationship between allergies and other diseases is just beginning to be understood.

Proper treatment of allergic rhinitis may be critical to controlling the comorbid conditions. A recent longitudinal study followed 783 students diagnosed with asthma or allergic rhinitis over 23 years of follow-up.[54] The resolution of allergic rhinitis symptoms correlated significantly with improvement in asthma (p=.0078), and worsening of allergic rhinitis was associated with the persistence of asthma symptoms. Far from the trivial nuisance symptoms allergic rhinitis was thought to represent 10-20 years ago, allergies are

now recognized as a complex, immunological response, frequently associated with other comorbid diseases and best managed taking an individualized approach to patient care.[4]

2.2.3. Patients May Miss Other Serious Diseases While Mistakenly Self Medicating for Allergies

With OTC self-medication, the initial stages of asthma, which may present with non-specific symptoms, are more likely to be missed. The effect of a delay in anti-inflammatory treatment of bronchial asthma is not completely clear, but there is some evidence that a delay in anti-inflammatory treatment may result in a permanent loss in lung function.[55–58] In addition, the lack, or delay, of appropriate asthma treatment may result in severe asthma attacks, which can be life threatening.

Numerous medical conditions in addition to asthma may present as self-diagnosed "allergy" but require a physician's history, physical, and further work-up for appropriate diagnosis and treatment. Allergists report the following conditions that commonly present as "allergy complaints": sinusitis, otitis, nasal polyps, and anatomic nasal obstruction (e.g., adenoids, septal deviation). The effectiveness of antihistamines in these associated diseases has not been established. More serious conditions not appropriately self-diagnosed include: pneumonia, cystic fibrosis, lung cancer, vasculitis, and various drug allergies.

Signs and symptoms of rhinal infections may be mistaken by the patient for symptoms of seasonal allergic and perennial allergic rhinitis. The risk associated with the non-indicated use of antihistamines in nasal and other upper respiratory infections has not been systematically evaluated. This is particularly relevant for more serious bacterial infections requiring antibiotic treatment, which include acute sinusitis and acute otitis media, which may eventually be diagnosed but for which treatment may be delayed. Otitis media is particularly a problem in preschool children in whom it may be associated with impaired hearing, learning difficulties, and even impaired language development.[59]

Even if a patient does have allergies, they may improperly estimate the seriousness of the allergies. OTC loratadine use in seasonal allergic rhinitis would be in line with the approved prescription use. However, a patient may have perennial allergic rhinitis, for which loratadine is not currently approved. The same is true for use in symptomatic treatment of the common cold, which represents inappropriate use.[60]

All of these scenarios represent unquantified but real risks associated with expanded OTC use of antihistamines. Data does not currently exist to accurately estimate these risks nor to determine definitively if they could be managed by appropriate patient labeling.

2.2.4. Recent Heightened Concerns About Patient Safety

Recent heightened concerns about patient safety also support exercising caution in considering moving a widely utilized R_x product to OTC status. Within the last two years, the Institute of Medicine (IOM) has issued two reports addressing patient safety and medical errors and barriers affecting the quality of health care in the U.S.[61] The initial report concluded that many medical errors result from misuse, overuse, and underuse of medications. The second report concluded that there is a need for improved communication and coordination of care, particularly considering that 40% of those with chronic conditions have more than one such condition. Placing each condition in individual "silos" diminishes optimal management. These findings raise issues that are of particular concern regarding the inappropriateness of moving prescription antihistamines to OTC status. This is based upon an appreciation of the importance of physician involvement in the treatment and management of chronic conditions such as allergies, particularly when inadequate or unsafe management of such conditions can lead to or exacerbate more serious diseases, such as asthma. To change from R_x to OTC status in effect means removing the physician from the process of managing this chronic condition and increases the opportunity for underuse, overuse, or misuse of medications to treat this disease. This flies in the face of the recommendations being made by experts in the safety debate.

2.3. The Safety Profile for OTC Use of the Second-Generation Antihistamines Has Not Yet Been Established

The safety profile for prescription use of loratadine and the other second-generation antihistamines has been established with physician oversight of concomitant medication and comorbid conditions. The use of these drugs on an OTC basis would present a number of potential issues not raised by prescription use, all of which require further study to establish

through scientific data that the drugs would have an appropriate risk-benefit profile for OTC use.

2.3.1. The Pharmacokinetic Interaction Profile of the Second-Generation Antihistamines Is Still Being Developed

The first of the second-generation antihistamines approved in the United States (terfenadine -- approved in 1985; astemizole – approved in 1988) were both withdrawn from the market because of rare but potentially life-threatening cardiac safety problems. Use of these drugs in combination with other products, or at levels above the recommended dose, caused QTc prolongation resulting in a potentially fatal cardiac arrhythmia called torsade de pointes. It took more than 10 years to fully recognize the safety problem with these products that ultimately resulted in their removal from the market. Critical to this process was that the products remained prescription products, with physician oversight playing an important role in adverse event reporting and identification of possible drug interactions.

In assessing cardiac safety, the two risk factors that have been identified by FDA for second-generation antihistamines are (1) prolongation of QTc in a dose-dependent fashion, and (2) pharmacokinetic interaction. With both terfenadine and astemizole there was a dose-dependent prolongation of QTc. High-dose cardiac studies for loratadine and fexofenadine did not show an increase in QTc.

The pharmacokinetic disposition of the second-generation antihistamines varies significantly from product to product. Cetirizine is not substantially metabolized and is essentially excreted unchanged in urine and feces. Loratadine undergoes first-pass metabolism. Formation of the major metabolite, desloratadine, is mediated by CYP3A4. Fexofenadine is poorly metabolized (<5%). Its disposition has been reported to be mediated by transport mechanisms found in the gut, liver, and kidneys (P-glycoprotein pump [P-gp] and Organic Anion Transport Polypeptide [OATP]).

The pharmacokinetic interaction profile of the second-generation antihistamines is complex, and far from being fully understood. When it was first noted that fexofenadine had an interaction with ketoconazole (potent CYP3A4 inhibitor), it was known that fexofenadine was not substantially metabolized by CYP3A4. It was only through further study that the role of transport proteins (e. g., P-gp and OATP) was recognized. In the gut OATP actively transports drug from the lumen into the portal system, while P-gp functions as a

counterpump to OATP. A drug whose absorption is dependent on OATP such as fexofenadine would interact with various fruit juices to decrease bioavailability.[62] However, the mechanism of the observed reduction of fexofenadine bioavailability caused by dietary salt is not understood.[63]

This area of clinical research is in its infancy and rapidly evolving. For example, the puzzling interaction observed between fexofenadine and ketoconazole has resulted in the use of fexofenadine as a probe substrate for uptake and efflux transport pumps in the gut, liver, and kidneys. Furthermore, it is also now known that CYP3A4 and P-gp are often co-localized in tissues. This complicates clinical interpretation of drug interactions that were formerly attributed to CYP3A4. Thus drug interactions previously identified and mechanistically thought to be understood, have to be re-evaluated.

Loratadine was approved in the United States in 1993, cetirizine in 1995, and fexofenadine in 1996. The safety issues associated with terfenadine were not fully understood until 1996 - more than ten years after initial approval in 1985. None of the currently marketed second-generation antihistamines have the serious safety issues associated with terfenadine or astemizole. Nevertheless, we are still learning new information about these products. The recent discovery of the P-glycoprotein pump and OATP has raised additional questions concerning drug interactions. Because the pharmacokinetic interaction and safety profiles of loratadine, cetirizine, and fexofenadine are different, each of the products must be considered individually. These questions are less cause for concern in the prescription context, where close physician care remains. However, the same safeguards and assurances would not exist for patients self-medicating, should problems arise. Ultimately, further study may be appropriate in this area, particularly before making the drugs available for OTC use.

2.4. Taking Second-Generation Antihistamines OTC May Result in Decreased Access and Will Not Necessarily Decrease the Use and Issues Associated with the First-Generation Antihistamines

While providing the opportunity for optimal treatment, the need to see a physician has not impeded patient access to second-generation antihistamines. Patients being prescribed loratadine typically see their physician at the beginning of the allergy season and receive, on average, a prescription for one month's supply of loratadine with 2 to 3 refills.[29]

This is normally sufficient medication for the allergy season and does not require additional visits to the physician.

Rather than increasing access, there is evidence that a switch to OTC status could adversely affect patient access to second-generation antihistamines. Blue Cross has already indicated that it will not reimburse for prescription drugs that have OTC equivalents in strength and dosage form. Moving second-generation antihistamines OTC will result in a cost shift to patients and away from medical insurers. Patients will experience a decrease in insurance coverage and a corresponding increase in out-of-pocket drug costs. Approximately 70% of the United States population have medical coverage that includes prescription drug coverage.[64] For this 70% of the population, an OTC switch may mean drug out-of-pocket costs will increase. Patients who can least afford this cost shift will be hurt the most by it, e.g., Medicaid patients.

This cost shifting will have major impact on certain subgroups.

- For patients with allergies and asthma, allergies are a very serious disease. Asthma accounts for 1.8 million emergency room visits yearly,[65] and asthma health care costs exceed 11.3 billion dollars per year.[66] Eighty-four percent of asthmatics presenting at emergency rooms have tested positive for common aeroallergens.[67] If second-generation antihistamines are taken OTC, the physician's presence in monitoring the allergy treatment and the total respiratory treatment of the asthmatic will be diminished. The result is the potential of increasing costly hospital visits.

- Many childhood illnesses are highly correlated with allergies. In addition to asthma, one prominent example is otitis media (estimated to cost $3.5 million annually). Fifty percent of children over age three with otitis media have confirmed allergic rhinitis[2] and allergy plays a major role in the reoccurrence of otitis media.

- Allergies are well recognized as having a large genetic component, and many families have multiple members affected.[28] A child has approximately a 29% chance of developing allergies if one parent has an allergic disorder,[68] and if both parents have the same type of allergy, the risk for the child is about 72%.[49] For these families, allergies are very serious diseases. If a family with two or three members, presently with insurance coverage, has the economic impact of paying 100% for out-of-pocket OTC medicines, and possibly increased physician visits shifted to it, the results would be dramatic.

Switching the second-generation antihistamines to OTC status is unlikely to result in an elimination of the issues associated with the first-generation antihistamine products. An analysis of the Canadian experience, where second-generation antihistamines are available OTC, shows that first-generation sedating antihistamine sales in the last 5 years continue to rise at an average annual rate of 4.1%.[69] In 2000, they still represent about one-third of all units sold. In contrast, the current U.S. market shows a very different picture. Second-generation antihistamines are growing at an average annual rate of 36.9%, while first-generation antihistamines are declining at an average rate of –2.8%.[70] The balance between second-generation antihistamines and first-generation antihistamines is better in the U.S. today than in Canada under their OTC system.

3. CONCLUSIONS

As the foregoing discussion demonstrates, additional study is needed to evaluate whether loratadine, fexofenadine hydrochloride, or cetirizine hydrochloride could be used safely and effectively without a physician's supervision. Numerous questions about OTC usage remain unanswered and require examination to responsibly evaluate the risks and benefits of providing loratadine, fexofenadine hydrochloride, and cetirizine hydrochloride in an OTC setting. Many of these questions need to be answered separately for each of the products.

Issues that should be addressed before any of these products is switched are listed below, and in many cases, studies would need to be conducted and data generated to address the issues properly.

- Characterize and quantify the impact of an OTC switch on the quality of care of patients with allergic disease that are known to have significant associated morbidity such as bronchial asthma, sinusitis, etc.
    - What percentage of patients taking OTC antihistamines would develop asthma exacerbations?
    - What percentage of patients taking OTC antihistamines would develop sinusitis?
    - What percentage of patients taking OTC antihistamines would develop otitis?
    - In what percentage of these patients would the outcomes of these events be more serious because of delays in diagnosis or delay in seeking appropriate medical care?
- What are the projections for general use of first-generation vs. second-generation antihistamines after an OTC switch? What are the public health implications?
- What are the effects on disease outcome specifically in asthmatics (long term and short term) when they self-medicate with antihistamines vs. under a physician's care?
- Loratadine is now largely prescribed as part of a chronic disease management process, but OTC use is necessarily oriented toward acute symptomatic relief. What are the long-term consequences of removing patients from the disease management approach of the current medical system?
- Do we need to further characterize the drug-interaction potential for each of the second-generation antihistamines?

- Label Comprehension Study – Current OTC antihistamine indications are for "temporary relief of sneezing, itchy, watery eyes, itchy throat, and runny nose due to hay fever and other upper respiratory allergies". These presumably may include patients with PAR in addition to SAR. Since loratadine and fexofenadine are not indicated for PAR, would there be inappropriate use? Can labeling ensure that patients properly differentiate allergic diseases from other diseases?

- Actual Use Study – This is needed to test appropriate patient self-selection for use and to ensure that appropriate dosing intervals are followed. Since loratadine is administered once daily and the current OTC market has primarily every-12-hour, or more frequent, dosing intervals, would consumers appropriately adapt to proper use of a once-daily product? The study should include "all comers" to follow outcomes in "inappropriate" self-selection and use.

- Colds Misuse Study – Current OTC antihistamines are used frequently to relieve symptoms of colds. With much less anticholinergic effect with loratadine than with first-generation antihistamines, will consumers use loratadine OTC in treatment of colds and increase the dose due to lack of efficacy?

- Outcomes Study – The R_x history of loratadine includes a very considerable percentage of patients requiring concomitant medications – whether for asthma or other comorbid conditions. Does the OTC availability of a mainstay R_x therapy in such patients lead to worse medical care and outcomes?

- Single-Dose Symptom-Relief Study – The primary use of OTC antihistamines is for "temporary symptomatic" relief. The OTC marketplace is much more oriented towards intermittent or episodic symptom relief than for chronic use. On the other hand, in the R_x setting, loratadine, fexofenadine, and cetirizine are frequently prescribed as part of a chronic disease-management approach, and efficacy is more reflective of steady-state dosing. What is the outcome of frequent one-time or episodic use versus use under a physician's care?

Until these questions are answered, the prescription status of the second-generation antihistamines should not be changed.

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